

Amendments to the Specification

Please replace the following paragraphs in the Specification:

Please replace the paragraph at page 5, lines 18 through 21 with the following amended paragraph:

Figure 2 shows the levels of oxidative burst of human neutrophils from ~~and~~ Kostmann patients (A=□, M=○), one patient with cyclic neutropenia (●) and a healthy donor (■). The assay records Fc dependant internalisation of a covalent complex of rabbit polyclonal anti-BSA and BSA with a fluorescence probe.

Please replace the paragraph at page 10, lines 3 through 4 with the following amended paragraph:

Preferably the agent which enhances synthesis of an antimicrobial ~~antimicrobial~~ agent enhances the synthesis of LL-37 and may be, for example, butyric acid.

Please replace the paragraph at pages 12, line 25 through page 13, line 2 with the following amended paragraph:

The control sample to which the levels of LL-37 in the individual under test are compared may be a sample from another subject having reduced levels of LL-37, for example another subject having a type of neutropenia associated with reduced LL-37 levels, preferably morbus Kostmann ~~morbus~~. The control sample may be a theoretical sample from a reference database of such subjects. The mean reduced level of LL-37 is used as the control value. Preferably, the control value is a range of LL-37 levels associated with that type of neutropenia. In this case a subject having a type of neutropenia associated with reduced LL-37 levels is a subject having the same or similar level to the control sample.

Please replace the paragraph at page 17, lines 2 through 11 with the following amended paragraph:

The present invention provides a product comprising LL-37 and a cytostatic drug, LL-37 and a corticosteroid or LL-37 and a growth differentiation factor for separate,

sequential or simultaneous use in the treatment of the human or animal body. The product is useful in the treatment of any disease that may be treated using the cytostatic agent, corticosteroid or growth/differentiation factor. Such diseases include neutropenia, malignant diseases and inflammatory diseases such as ulcerative colitis and Crohn's disease. ~~Patients~~~~Patient's~~ with bone marrow transplants may also be treated using the product. In such treatments the amount of LL-37 administered in combination with the corticosteroid or cytostatic agent is ~~00~~ an amount effective to counteract the side effects of the corticosteroid or cytostatic agent.

Please replace the paragraph at page 18, lines 1 through 12 with the following amended paragraph:

Accordingly a method of treating a disease selected from neutropenia, malignant diseases and inflammatory diseases is also provided. A method of treating a bone-marrow transplant patient is also provided. The method typically comprises administering to a subject in need thereof, a therapeutically effective amount of a cytostatic agent or corticosteroid and an amount of LL-37 effective to reduce susceptibility to infection. A therapeutically effective amount of a cytostatic agent or corticosteroid is an amount which will reduce one or more ~~symptoms~~symptoms of the disease or generally alleviate the condition of the patient. An amount of LL-37 effective to reduce susceptibility to infection is an amount that will attack an infection-causing microbe entering the body such that so that no symptoms or less severe symptoms of infection by the microbe are observed.

Please replace the paragraph at page 19, lines 21 through 28 with the following amended paragraph:

Where LL-37 mRNA is detected, a probe or primer that hybridises to the mRNA sequence may be used in a detection method. The probe or primer typically has a sequence complementary to the mRNA sequence but may contain one or more mismatch providing that under the hybridising conditions used in the assay, the probe or primer binds specifically to the LL-37 mRNA.[[.]] A probe or primer "specifically binds" to LL-37 mRNA when it binds with preferential or high affinity to LL-37 mRNA but does

substantially bind, does not bind or binds with only low affinity to other mRNA sequences.

Please replace the paragraph at page 22, lines 15 through 24 with the following amended paragraph:

All four Kostmann patients were diagnosed before the age of 5 months and with typical clinical findings. Two additional and unrelated patients with congenital neutropenia were included in the study: one with a more mild form of Kostmann-like syndrome (she was 5 years of age at diagnosis and was referred because of chronic gingivitis) and one with cyclic neutropenia. All patients had periodontitis before G-CSF treatment started, except for the patient with cyclic neutropenia, though these patients can suffer also from this affliction. Out of 22 controls, 19 were relatives and 3 were unrelated healthy individuals. The patients, their relatives and one healthy control donated their blood at the Pediatric Ward of Sunderby hospital, Luleå, Sweden. Ethical permission was granted (Umeå, dnr 01-250).

Please replace the paragraph at page 23, lines 11 through 20 with the following amended paragraph:

Plasma and extracts from neutrophils respectively were mixed with sample buffer and heated at 90°C for 3 min. Proteins were separated on a 10-20% Tris-Tricine SDS-acrylamide gel (Novex) and blotted onto PVDF-filters (Novex). The filters were blocked for 1h with 5% milk powder in PBS/0.1% Tween 20 (PBST). Filters were washed and incubated over night with anti-LL-37 antibody 1:10 000 dilution and after washing with secondary anti-rabbit serum coupled to HRP (BioRad) for 1h in PBST. After additional washings, detection was by ~~chemiluminescence~~~~chemiluminescence~~ using ECL plus (Amersham Pharmacia Biotech AB, Sweden). When the anti-cathelin-peptide antibody was used, the samples were reduced in 5% 2-mercaptoethanol (80°C / 10 min) before electrophoretic separation.

Please replace the paragraph at page 24, lines 8 through 17 with the following amended paragraph:

Although neutrophil counts may vary with time, plasma level of cathelin-LL-37 is normally present in concentrations around 1.2 µg/ml. Our Western blot analysis (Figure 1, right part) shows that the patients T, M and A had 1-2% of normal plasma levels of cathelin-LL-37, estimated by densitometric scanning. The sporadic patient (J) had a 5-10-fold higher level than the Kostmann patient (which equals 10% of controls) and the ~~transplanted~~transplanted patient (N) had close to normal levels (70% of controls). The same pattern of cathelin-LL-37 in patients and controls was obtained in Western blot analysis with an antibody directed against the cathelin part of the precursor. No free LL-37 could be detected in any of the samples even after a prolonged exposure.

Please replace the paragraph at page 24, lines 25 through 32 and page 25, lines 1 through 4 with the following amended paragraph:

Peptides/proteins from the neutrophil enriched cell preparation were extracted in 30% acetic acid for 2.5h~~2.5h~~ at +4°C and centrifuged. The supernatant was lyophilized and resuspended in 0.1% trifluoroacetic acid and centrifuged. The clear supernatant was analysed by analytical HPLC using a C18 column (Vydac, 218TP54, The Separation group, Hesperia, USA) and acetonitrile/water gradients from 10-60 %. The elution position of defensins (HNP 1-3) was identified by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry using a Reflex III (Bruker Daltronics, Germany). The peak area under the curve was calculated, translated to µg using purified defensin HNP 1 standard curves, compensated for the difference in loading and finally related to number of neutrophils and presented as µg of defensin/ 10⁶ neutrophil. HNP-1 was kindly donated by Dr.R. Lehrer, UCLA, USA.